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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/365,677	LAM ET AL.	
	Examiner	Art Unit	
	Anne Baker	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment filed December 4, 2001 (Paper No. 6) has been entered. Claims 1-16 have been amended.

Claims 1-17 remain pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Specification

The disclosure is objected to because of the following informalities:

The use of the trademark LASERSKIN™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

See, for example, page 4, line 31, page 7, lines 11-29, and the Abstract at page 18, line 9. Applicant is reminded that the entire specification should be reviewed and corrected.

The use of a trademark coupled with the word "type" should be avoided. See MPEP 608.01(v). The instant specification uses the term "Laserskin type material" at page 11, lines 12-13.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method wherein the cultivated skin material comprises a layer of keratinocytes upon an upper side of a biosynthetic substratum of an esterified hyaluronic acid, does not reasonably provide enablement for the claimed method wherein the cultivated skin material comprises a layer of keratinocytes upon an upper side of a substratum, wherein any type of material is employed as the substratum. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to provide an enabling disclosure for the use of any type of material as the "substratum" recited in the claims. The specification only teaches how to use a biosynthetic substratum of an esterified hyaluronic acid. The art clearly discloses the unpredictability of 'take' rates when using different materials in composite skin grafts and in using different configurations of the materials, e.g., varying the cell types used on or within the biocompatible synthetic material. For example, Cooper et al. (1993) directly compare a cultured composite skin substitute containing human keratinocytes and fibroblasts to an epidermal sheet graft containing human keratinocytes. They demonstrated significant advantages of the composite graft over the epidermal sheet graft in the closure of full-thickness wounds.

Thus, given the unpredictability in the art for successfully employing various synthetic materials in skin graft composites and further given the limited teachings in the specification directed to using a biosynthetic substratum of an esterified hyaluronic acid, the skilled artisan would have been required to

engage in undue experimentation to practice the claimed invention over the full scope, wherein any type of material is used as the substratum for support of a layer of keratinocytes.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 are indefinite in their recitation of the phrase "target donor patient" because it is unclear how the term "target" is being used to modify the term "donor patient." It is unclear how a "target donor patient" differs from any other "donor patient." The metes and bounds of the claims are not clearly set forth.

Claims 1-6, 8-13, and 15-17 are indefinite in their recitation of the terms "layer" and "over" throughout the claims, in light of Applicants statement at page 11, paragraph 1 of the response, which unequivocally states that "the keratinocytes and dermal fibroblasts according to the present invention are in the same plane." For example, Claims 1-6 and 8-13 recite "layer of keratinocytes" and "layer of dermal fibroblasts" and further recite that the "layer of keratinocytes" are grown "**over**" said dermal fibroblasts. Thus, it is unclear how the keratinocytes and fibroblasts can be understood to be in the same plane if the layer of keratinocytes is **over** the fibroblasts.

Claims 4-6 are indefinite in their recitation of "said second dermal fibroblast layer" because the phrase lacks antecedent basis. Use of the phrase "said second layer of dermal fibroblasts" is suggested.

Claims 7 and 14 are indefinite in their recitation of "a substratum of a biosynthetic substratum" because the claim language appears to be pointing to a specific portion of a biosynthetic substratum, but it is unclear what portion would constitute "a substratum of a biosynthetic substratum."

Claim 8 is indefinite in its recitation of the term "compromising" in line 1. Use of the term "comprising" is suggested. Claims 9 and 10 are indefinite in so far as they depend from Claim 8.

Claim 16 is indefinite in its recitation of "an upper side of a biosynthetic substratum" because Claim 15 refers to the same element as "an upper side of a substratum" which is broader in scope than "an upper side of a biosynthetic substratum" as recited in Claim 16. However, Claim 16 is clearly referring to the same element as that of Claim 15 since the keratinocytes are on top of the dermal fibroblasts which are on top of the biosynthetic substratum.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 8 stand rejected and Claims 7 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Della Valle et al., 1997 (US Patent No. 5,658,331), for reasons of record advanced on pages 4-5 of the Office Action of Paper No. 4 (mailed 6/20/01).

Claim 1 is directed to a method for cultivating graftable skin by co-culturing fibroblasts and keratinocytes on a biosynthetic substratum, wherein said substratum is an esterified hyaluronic acid. Claim 7 is directed to a method for cultivating graftable skin by growing a layer of keratinocytes on a biosynthetic

substratum, wherein said substratum is an esterified hyaluronic acid. There is no requirement for fibroblast feeder cells, although the claim encompasses the embodiment where fibroblast feeder cells are present. Claim 8 is directed to a graftable skin material comprising a layer of keratinocytes over a layer of dermal fibroblasts on the upper side of a biosynthetic substratum of an esterified hyaluronic acid. Claim 14 is directed to a graftable skin material comprising a layer of keratinocytes on the upper side of a biosynthetic substratum of an esterified hyaluronic acid. There is no requirement for fibroblast feeder cells, although the claim encompasses the embodiment where fibroblast feeder cells are present.

At page 7, paragraph 1 of the response, Applicants point out that Della Valle et al. (1997) use 3T3 fibroblasts (a mouse cell line) in Example 3 and Applicants argue that there have been no reports about the use of human cells, either autologous or allogeneic dermal fibroblasts, as a feeder layer for cultivation of keratinocytes on culture dishes or substratum such as those of the present invention, including Laserskin™. However, the claims do not require the use of **human** dermal fibroblasts as the feeder layer. The claims merely recite "a layer of dermal fibroblasts." Applicants are arguing limitations not in the claims.

At page 7, paragraph 1 of the response, Applicants assert that Hyaff™ is structurally different from the substratum of the present invention. No support is offered for this assertion. The "substratum of the present invention" is that which is recited in the claims. The claims recite "a biosynthetic substratum of an esterified hyaluronic acid." Della Valle et al. (1997) disclose at Column 4, lines 66-67, that HYAFF 11 membranes consist of "hyaluronic acid benzyl ester with 100% esterification." Thus, Hyaff™ constitutes the substratum of the present invention as it clearly meets the claim limitation reciting "a biosynthetic substratum of an esterified hyaluronic acid."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 9, and 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Della Valle et al. (1997) and Hansbrough et al. (1989), for reasons of record advanced on page 6 of the Office Action of Paper No. 4 (mailed 6/20/01).

At page 8, paragraph 2 of the response, Applicants argue that Della Valle et al. (1997) use 3T3 cells, but not human dermal fibroblasts as a feeder layer. However, the claims do not require the use of **human** dermal fibroblasts as the feeder layer.

Although Della Valle et al. (1997) does not teach using allogenic or autologous fibroblasts in the graftable skin material, Hansbrough et al. (1989) does. At page 2126 of Hansbrough et al. (1989) autologous human fibroblasts and keratinocytes were obtained from a burned patient and used to prepare graftable skin material on a collagen-glycosaminoglycan (collagen-GAG) membrane.

At page 9, paragraph 1 of the response, Applicants argue that Hansbrough et al. (1989) do not teach or suggest a co-culture of autologous fibroblasts and keratinocytes, because in their work keratinocytes and dermal fibroblasts were grown in different layers of the collagen-GAG. However, Della Valle et al. (1997) already teach the co-culture of fibroblasts and keratinocytes on an esterified hyaluronic acid substratum, as recited in the claims, and Hansbrough et al. (1989) is relied upon only for providing evidence that it was well-established in the art to use autologous fibroblasts and keratinocytes in preparing graftable skin material. Applicants further argue that the collagen-GAG matrix used by Hansbrough et al.

(1989) is very different from the Laserskin™ (an esterified hyaluronic acid substratum) used in the present invention. However, Della Valle et al. (1997) provides this teaching. Della Valle et al. (1997) teaches the use of a benzyl esterified hyaluronic acid substratum having a layer of keratinocytes seeded over a layer of mouse 3T3 fibroblasts. Hansbrough et al. (1989) is relied upon only for providing evidence that the art recognized the advantages of using autologous fibroblasts and keratinocytes in the context of preparing graftable skin material.

At page 9, paragraph 2 of the response, Applicants argue that the present invention requires that both the upper and basal sides of the biosynthetic substratum are seeded with dermal fibroblasts. However, this is incorrect. The rejected claims do not recite the limitation that the basal side of the substratum is seeded with dermal fibroblasts.

Sufficient motivation to combine the references has been provided, in that the skilled artisan would have recognized the advantage of using autologous fibroblasts and keratinocytes (as taught by Hansbrough et al., 1989) for avoidance of an immune response and graft rejection.

Claims 11-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Della Valle et al. (1997) in view of Cooper et al. (1993), Hansbrough et al. (1989), and Myers et al. (1997), for reasons of record advanced on pages 7-9 of the Office Action of Paper No. 4 (mailed 6/20/01).

At page 10, paragraph 4 of the response, Applicants argue that Cooper et al. (1993) do not teach seeding keratinocytes on a substratum according to the present invention, such as Laserskin™. However, Della Valle et al. (1997) provides this teaching.

At page 11, paragraph 1 of the response, Applicants argue that, according to Cooper et al. (1993) the keratinocytes seeded on the uppermost laminated surface were not in the same planar surface of pre-

seeded dermal fibroblasts, whereas the keratinocytes and dermal fibroblasts according to the present invention are in the same plane. Applicants are arguing limitations that are not in the claims. The claims do not recite the limitation that the keratinocytes and dermal fibroblasts must be in the same plane. On the contrary, the claims repeatedly recite phrases such as "layer of dermal fibroblasts" and "layer of keratinocytes" and further explicitly recites that the "layer of keratinocytes" is **over** the dermal fibroblasts. Applicants statement that "the keratinocytes and dermal fibroblasts according to the present invention are in the same plane" calls into question the meaning of the terms "layer" and "over" as recited throughout the claims (see rejection above under 35 U.S.C. 112, second paragraph).

At page 11, paragraph 2 of the response, Applicants argue that Myers et al. used irradiated, non-proliferating mouse 3T3 cells and that the present invention uses non-irradiated, proliferating human dermal fibroblasts. Applicants are again arguing limitations that are not in the claims. Claims 11-13 do not recite the limitation that the fibroblasts are **proliferating** nor that they are **human** fibroblasts. Thus, the non-proliferating mouse 3T3 cells meet the limitations of the claims.

At page 11, paragraph 3 of the response, Applicants argue that prior to the present invention, no one had replaced 3T3 cells with non-irradiated, proliferating human fibroblasts and that there was no expectation that irradiated, nonproliferating, xenogeneic 3T3 cells could be successfully replaced with non-irradiated, proliferating human fibroblasts. Again, Applicants are arguing limitations that are not in the claims. The claims do not recite the limitation that the fibroblasts are **proliferating** nor that they are **human** fibroblasts. Thus, Claim 11 clearly reads on the use of irradiated 3T3 cells. Further, Hansbrough et al. (1989) clearly discloses the successful use of **autologous**, **proliferative human** fibroblasts and **human** keratinocytes (page 2126, column 1, lines 9-11) in preparing graftable skin material in 1989.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER